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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,126	02/22/2002	Gerald W. DeVries	P-AR 4951	8539

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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,126	DEVRIES, GERALD W.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *39,40 and 45-57* is/are rejected.

7)☒ Claim(s) *41-44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 39-57 are pending.

2. In view of the amendment filed 2/27/06, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39-40 and 45-57 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method of extending corneal graft survival following corneal transplantation in a patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising a vascular endothelial growth factor receptor-3 kinase inhibitor selected from the group consisting of 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) and 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51), (2) The said method further comprising administering to said patient an anti-angiogenic agent or an immunosuppressive agent, **does not** reasonably provide enablement for a method of extending corneal graft survival following corneal transplantation in any patient comprising administering to said patient an effective amount of a pharmaceutical composition comprising (1) *any* "VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) *any* immunosuppressive agent, wherein the pharmaceutical composition is administered prior to, or subsequent to corneal transplantation, two or more times, over a period of at least one or six months as set forth in claims 39-40, and 45-57. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only three VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structures as shown on page 56 and a method of extending corneal graft survival in a rat model of karetoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51). The specification discloses that transplantation of corneas from Lewis strain rats to Wistar-Furth recipients, where rats receiving only vehicle demonstrate evidence of graft rejection, on average, at day 30. In contrast, in animals receiving MAE87, MAE106 or MAZ51 exhibit increased mean graft survival as demonstrated by a significant delay in evidence of graft rejection.

The specification does not teach how to make any and all "indolinone VEGFR-3 kinase inhibitor" and any "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain without the chemical structure and/or amino acid sequence that correlated with the functions for the claimed method of extending corneal graft survival following corneal transplantation in a human. The specification does not teach how to make any inhibitor mentioned above because there is insufficient guidance with respect to the structure without the amino acid sequence, or chemical structure of *all* "VEGFR-3 kinase inhibitor" such as *all* "ATP analog", or *any* "VEGFR-3 inhibitor drown regulates VEGFR-3 expression", *any* "anti-angiogenic agent", or *any* "immunosuppressive agent", let alone which undisclosed ATP analog would bind to VEGFR-3 catalytic domain and function to inhibit lymphangiogenesis, and thereby extending corneal graft survival. Even if the inhibitor binds to VEGFR-3, binding does not equal to inhibiting lymphangiogenesis, in turn, useful for extending corneal graft survival. Likewise, inhibiting VEGFR-3 expression does not equal to extending corneal graft survival without sufficient working example. Even if the inhibitor binds to VEGFR-3, binding does not necessary mean down regulating VEGFR-3 expression.

Stryer *et al*, of record, teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent, there is insufficient in vivo working example demonstrating the efficacy of the claimed method. Given the unlimited number of undisclosed indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor that binds to the VEGFR-3 catalytic domain, anti-angiogenic agent, and immunosuppressive agent and without the structure, it is unpredictable which undisclosed indolinone VEGFR-3 kinase inhibitor in combination with which undisclosed anti-angiogenic agent and/or immunosuppressive agent is effective for the claimed method. Until the indolinone VEGFR-3 receptor kinase inhibitor and anti-angiogenic agent or immunosuppressive agent have been identified, the specification as filed merely invites one of skill in the art for further experimentation to arrive at the scope of the claimed invention.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 2/27/06 have been fully considered but are not found persuasive.

Applicants' position is that the issue is not whether the Applicants have enabled a method using any VEGFR-3 kinase inhibitor (although the Applicants maintain that they have). The pending claims are not directed to "any inhibitor", but are directed, instead, to a method using a

pharmaceutical composition comprising an "indolinone vascular endothelial growth factor receptor-3 inhibitor (VEGFR3). The Applicants' invention is broader than that, and the specification describes more, but all of the pending claims require indolinones. What matter is whether the specification enables the pending claims, all of which require indolinones. One can arrive at them through experimentation: even "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." The specification discloses three indolinone VEGFR-3 kinase inhibitors, MAE87, MAE106, and MAZ51. The specification describes methods useful in the invention include specific VEGFR-3 kinase inhibitors such as indolinoes that differentially block VEGF-C and VEGF-D induced VEGFR-3 kinase activity compared to that of VEGFR-2.... Additional VEGFR-3 kinase inhibitors, including specific, selective and non-selective inhibitors, are known in the art or can be identified using one of a number of well known methods for assaying for receptor tyrosine kinase inhibition such as ELISA assay to analyze the production phosphorylated tyrosine, see specification paragraphs 43-44. The skill of the art here is quite high (those who practice it usually have advanced degrees and extensive knowledge); the experimentation required is simple and routine, involving well-known assays and methods and the specification provides guidance as to which molecules work best, the indolinones required by the claims.

In response, enablement is not commensurate with the scope of the claimed method in which any indolinone is VEGFR-3 kinase inhibitor and is effective for extending corneal graft survival following corneal transplantation. The specification discloses only three specific indolinones vascular endothelial growth factor receptor-3 inhibitor (VEGFR3) such as MAE87, MAE106 or MAZ51 that recited in claims 41-44. Other than those three specific indolinones VEGFR-3 kinase inhibitors for the claimed method, there is insufficient guidance as to the structure of any other indolinones vascular endothelial growth factor receptor-3 inhibitor for the claimed method. This is because indolinone is a class of chemicals in itself. The specification does not disclose any assays that is predictive of in vivo success. The specification at pages 21 and 43-44 merely extends an invitation to one skill in the art to further experimentation to come up with other chemical from the class of indolinone and then see whether the undisclosed indolinones are effective for in vivo use. In contrast to applicant's assertion that the experimentation required is simple and routine, it is not routine to administer any VEGFR-3 kinase inhibitor from the class of indolinone chemicals for extending corneal graft survival

following corneal transplantation without knowing the pharmacokinetics of the compound. The specification does not provide any guidance as to which chemical substituents within which position of the indolinone moiety to be substitute and still maintains its structure/configuration and functions. The specification does not provide any guidance as to which chemical substituents to be substitute in the class of indolinone that would resulted in a selective inhibitor of VEGFR-3 kinase. Given the unlimited number of indolinones for the claimed method, there is insufficient in vivo working example demonstrating the class of indolinones can be generalize for the claimed method. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention.

5. Claims 39-40 and 45-57 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* and *all* "indolinone VEGFR-3 kinase inhibitor", whereby lymphagiongenesis is suppressed in the cornea of said patient, (2) *any* "VEGFR-3 kinase inhibitor" that binds to theVEGFR-3 catalytic domain, (3) the said method further comprises administering any anti-angiogenic agent, and/or (4) any immunosuppressive agent for the claimed method as set forth in claims 39-40 and 45-57.

The specification discloses only three indolinone VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival in a rat model of karetenoplasty following corneal transplantation by administering a pharmaceutical composition comprising 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) that extends corneal graft survival in rat.

The specification defines the term "VEGFR-3 kinase inhibitor" means an inhibitor of receptor tyrosine kinase that selectively or non-selectively reduces the tyrosine kinase of a VEGF-3 receptor such as an inhibitor that reduces VEGFR-3 tyrosine kinase activity without significantly effecting VEGFR-3 expression or other VEGFR-3 activity (page 20). The VEGFR-

3 kinase inhibitor can be *any* molecule that directly binds the VEGFR-3 catalytic domain, such as ATP analog. However, binding does not equal to function. Without a clear and adequate description about the structure associated with function of the genus of indolinone VEGFR-3 kinase inhibitor, VEGFR-3 kinase inhibitor, anti-angiogenic agent and immunosuppressive agent, the method of using a genus of VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent is not adequately described.

The specification discloses only three specific indolinones VEGFR-3 kinase inhibitors for the method of extend corneal graft survival, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of indolinones, and VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/27/06 have been fully considered but are not found persuasive.

Applicants' position is that the issue is not whether the specification describes "any VEGFR-3 kinase inhibitor" (although the specification does describe them). The pending claims are directed, instead, to a method using a pharmaceutical composition comprising an "indolinone VEGFR-3 kinase inhibitors". All of the claims require indolinones. The issue, therefore, is whether the specification describes a method using indolinone VEGFR-3 kinase inhibitors. One need not describe each and every antibody that binds the antigen. Describing a particular structure (an antigen) and a desired function (binding to an antibody) is sufficient. The principal rationale underlying this result is that antibodies are well known in the art. The specification and claims at issue here comport with the written description for similar reasons.

In response, the issue here is whether the specification describe any and all an "indolinone VEGFR-3 kinase inhibitors", any and all VEGFR-3 kinase inhibitor for the claimed method. The specification discloses only three indolinones VEGFR-3 tyrosine kinase inhibitors 3(2,4-dihydroxy-benylidene)-1,3-dihydroindol-2-one (MAE87), 3-3(fluoro-4methoxy-benzylidene)-1,3-dihydro-indol-2one (MAE106) or 3-(4-dimehylamino-naphthalen-1-

ylmethylene)-1,3-dihydro-indol-2-one (MAZ51) having the structure as shown on page 56 and a method of extending corneal graft survival. Other than those three indolinones mentioned above, there is inadequate written description about structure of any other chemical in the class of indolinones. The specification does not adequate describe the chemical substituents within which position of the indolinone moiety to be substitute and still maintains its structure/configuration and functions. The specification defines the term "VEGFR-3 kinase inhibitor" means an inhibitor of receptor tyrosine kinase activity that selectively or non-selectively reduces the tyrosine kinase activity of a VEGFR-3 receptor. Such an inhibitor generally reduces VEGFR-3 tyrosine kinase activity without significantly effecting the expression of VEGFR-3 and without effecting other VEGFR-3 activities such as ligand-binding capacity. A VEGFR-3 kinase inhibitor can be a molecule that directly binds the VEGFR-3 catalytic domain, for example, an ATP analog. VEGFR-3 kinase inhibitors useful in the invention include specific VEGFR-3 kinase inhibitors such as indolinones that differentially block VEGF-C and VEGF-D induced VEGFR-3 kinase activity compared to that of VEGFR-2. Such specific VEGFR-3 kinase inhibitors, for example, MAE106 and MAZ51. The specification does not describe any "ATP analog", the chemical structure and substituents (R groups) to be substitute such that the resulting "ATP analog" binds to VEGFR-3 catalytic domain, or any nonspecific VEGFR-3 kinase inhibitor for the claimed method. Further, the term "a VEGFR-3 kinase inhibitor" recited in claims 49 and 52 are any VEGFR-3 kinase inhibitor, and not the specific indolinone VEGFR-3 kinase inhibitor as argued because the claims recite "a" instead of "the" indolinone.

The specification discloses only three specific indolinones VEGFR-3 kinase inhibitors for the method of extend corneal graft survival, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of indolinones, and VEGFR-3 kinase inhibitor, anti-angiogenic agent and/or immunosuppressive agent to describe the genus for the claimed method. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

6. Claims 41-44 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

10. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 13, 2006

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